PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61B 5/0402

A1

(11) International Publication Number: WO 00/28893

(43) International Publication Date: 25 May 2000 (25.05.00)

(21) International Application Number: PCT/US99/27340

(22) International Filing Date: 18 November 1999 (18.11.99)

(30) Priority Data:
09/193,971 18 November 1998 (18.11.98) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 09/193,971 (CON)
Filed on 18 November 1998 (18.11.98)

(71) Applicant (*for all designated States except US*): NEW ENGLAND MEDICAL CENTER HOSPITALS, INC. [US/US]; 750 Washington Street, Boston, MA 02111 (US).

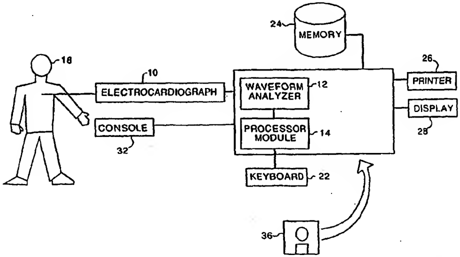
(72) Inventors; and
(75) Inventors/Applicants (*for US only*): SELKER, Harry, P. [US/US]; 155 Hampshire Road, Wellesley, MA 02181 (US). GRIFFITH, John, L. [US/US]; 11 Wilogreen Road, Natick, MA 01760 (US). BESHANSKY, Joni, R. [US/US]; 4 Brandywyne, Wayland, MA 01778 (US).

(74) Agent: MEIKLEJOHN, Anita, L.; Fish & Richardson, P.C., 225 Franklin Street, Boston, MA 02110-2804 (US).

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: A DIAGNOSTIC TOOL USING A PREDICTIVE INSTRUMENT



(57) Abstract

This invention is a method for evaluating a medical condition of a patient including the steps of monitoring one or more clinical features of a patient (18) based on the monitored features, computing a primary probability of a medical outcome or diagnosis via a waveform analyzer (12), and processor module (14); computing a plurality of conditional probabilities for a selected diagnostic test, the computed conditional probabilities including a first probability of the medical outcome or diagnosis assuming the selected diagnostic test produces a first outcome and a second probability of the medical outcome or diagnosis assuming the selected diagnostic test produces a second outcome; and displaying the computed primary probability on a display (28) as well as the plurality of computed conditional probabilities to a user as an aid to determining whether to administer the selected diagnostic test to the patient.

A DIAGNOSTIC TOOL USING A PREDICTIVE INSTRUMENT

Background of the Invention

The invention relates to predictive instruments for computing a patient's probability of a serious medical condition.

A number of instruments have been developed that enable the physician to compute probabilities of life threatening cardiac conditions for patients. Some of these instruments are described in the following references, all of which are incorporated herein be reference.

A hand-held predictive instrument is described by Michael W. Pozen et al. in "A Predictive Instrument to Improve Coronary-Care-Unit Admission Practices in Acute Ischemic Heart Disease" The New England Journal of Medicine, Vol 310 pp. 1273-1278, May 17, 1984. With the handheld calculator-based instrument, a physician can compute a patient's probability of having acute cardiac ischemia based upon physician-entered values for a set of clinical variables. An automatic, computerized version of this instrument which utilizes output from a electrocardiograph and a waveform analyzer is described by H.P. Selker et al. in "A Time-Insensitive Predictive Instrument for Acute Myocardial Infarction Mortality", Med. Care 1991; 29:1196-1211.

A predictive instrument for determining the probability of acute hospital mortality of a cardiac patient is described in U.S. 4,957,115 to Dr. Harry P. Selker, and incorporated herein by reference. The probability of acute hospital mortality is commonly understood to mean the probability of dying from a current acute condition, generally during the specific initial hospitalization for the problem. It is also

a second probability of the medical outcome or diagnosis assuming the selected diagnostic test produces a second outcome; and displaying the computed primary probability as well as the plurality of computed conditional probabilities to a user as an aid to determining whether to administer the selected diagnostic test to the patient.

Preferred embodiments include the following features. The step of monitoring involves monitoring EKG-related characteristics of the patient, wherein the computed primary probability is a probability of a cardiac problem, and wherein the selected diagnostic test is selected from the group consisting of a CK blood test, an ETT, a stress test, and Sestamibi scanning test. The method also includes the step of computing a second plurality of conditional probabilities for a second selected diagnostic test, the second conditional probabilities including a first probability of the medical outcome or diagnosis assuming the second selected diagnostic test produces a first outcome and a second probability of the medical outcome or diagnosis assuming the second selected diagnostic test produces a second outcome. Alternatively and/or in addition, the method includes computing a second plurality of conditional probabilities for a second selected diagnostic test, the second plurality of conditional probabilities assuming a particular outcome of the first-mentioned selected diagnostic test, the second conditional probabilities including a first probability of the medical outcome or diagnosis also assuming the second selected diagnostic test produces a first outcome and a second probability of the medical outcome or diagnosis also assuming the second selected diagnostic test produces a second outcome.

In general, in another aspect, the invention is a method for determining a diagnostic test plan for a

test results are in-hand, but more importantly,by providing estimates of the potential probabilities that would result based on the possible results of a particular diagnostic test, it also gives the clinician accurate advice and guidance as to which of the diagnostic tests would be most helpful in diagnosing the seriousness of patient's condition.

Other advantages and features will become apparent from the following description of the preferred embodiment and from the claims.

Brief Description of the Drawings

Fig. 1 is a block diagram of a diagnostic system which computes and presents an array of conditional probabilities of acute cardiac ischemia;

Fig. 2 is an example of a printout from the system illustrated in Fig. 1;

Fig. 3 presents the coefficients and variables of an example of a logistic regression equation used to predict a particular cardiac outcome, e.g. the probability of acute cardiac ischemia; and

Fig. 4 presents the coefficients and variables of an example of a logistic regression equation used to compute a conditonial probability, e.g. the probability of acute cardiac ischemia assuming that that a CK test results are available.

Description of the Preferred Embodiments

Referring to Fig. 1, a predictive instrument constructed in accordance with the invention includes a 12-lead electrocardiograph 10, a waveform analyzer 12, and a programmed processor module 14. Electrocardiograph 10 is connected to a patient 18 and produces a set of ECG waveforms for the patient. Waveform analyzer 12 is programmed to analyze the ECG waveforms and recogni

test given the results of the preceeding ECG and CK tests.

The processor module displays the computed probabilities in a form and manner that is designed to be most useful to the physician using the predictive instrument. Typically, the results are printed across the top of the ECG waveform trace output that is also generated by the electrocardiograph so that a permanent record of them is generated for the patient's file and so that they are available in a convenient readily accessible form for the physician. Alternatively, or in addition, the results can be displayed in some other fashion such as through the video monitor that is part of the instrument.

In this example, the significance of the information which is communicated to the physician is as follows. Based upon the monitored ECG waveform and the presenting information that is obtained from the patient, the computed probability of acute cardiac ischemia (ACI) is 42%. In other words, among the people that were represented in the database that was used to generate the regression equation, 42% of those people who had similar characteristics were actually experiencing ACI.

Besides presenting this initial information, the report also presents the physician with guidance regarding what further tests to perform on the patient in order to most effectively and efficiently decide whether the patient's likelihood of acute cardiac ischemia is such that he or she should be admitted to the hospital or allowed to go home. The guidance is in the form of the predicted conditional probabilities for each of two tests that could be performed on the patient, namely, a CK blood test and an ETT. If a CK blood test is performed and the results are positive, the computed probability of ACI will increase to 85%. That would be high enough to

from one patient to the next. The Pagewriter XLi includes an internal computer that can be programmed to perform the appropriate waveform analysis. For example, it can be programmed to recognize and quantify the presence of key features within the ECG waveform. It can also be programmed to identify the location of a myocardial infarction (MI) based on the characteristics of the set of signals produced by the twelve monitoring leads. Besides performing the wave analysis functions, the computer within the unit can also be programmed to perform the functions of other components or modules within the system, e.g. the computations of the predictive instrument.

In the described embodiment, processor module 14 uses logistic regression-based equations for computing the probabilities that the patient is experiencing acute cardiac ischemia. For further descriptions of predictive instruments which are capable of computing probabilities of ACI or other medical problems and which can be used in connection with the present invention refer to the following patents, all of which are incorporated herein by reference: U.S. 4,957,115 by Selker, entitled Device for Determining the Probability of Death of Cardiac Patients"; U.S. 4,998,535 by Selker et al., entitled "Thrombolysis Predictive Instrument"; U.S. 5,277,188 by Selker, entitled "Clinical Information Reporting System"; and U.S. 5,501,229, 5,718,233 and U.S. 5,724,983, all three of which are by Selker et al., and are entitled "Continuous Monitoring Using A Predictive Instrument".

The logistic regression equations are of the following general form:

$$P = 100\left[1 - \frac{1}{1 + e^{z}}\right]$$

the x_i's can take for the different variables. Note that only the largest value for x is used per variable. Also ECG findings must be present in at least two leads, and S-T segment and T wave changes are "normal" if secondary to right or left complete bundle branch blocks, left ventricular hypertrophy, or a paced QRS. Only one type of abnormality is coded each for S-T segment and for T wave per patient (exclusive of TWISTDEP), use with elevation taking priority. Deviations are expressed in mm using the standard ECG scale of 1mm = 0.1 mV.

In the above-described embodiment of the present invention, each level of conditional probabilities is computed using a corresponding different logistic regression equation. Each regression equation is derived using the same approach that was used to derive the regression equation illustrated in Fig. 3. However, at least one additional explanatory variable is added to account for the test that is being modeled by the regression equation. In the equation which incorporates the CK blood test results, those test results are represented as an additional dichotomous variable (e.g. an additional $b_j x_j$ term in the regression equation). Similarly, in the equation which incorporates the ETT test results, those results are also represented by at least one additional dichotomous variable.

An example of the variables which would appear in the logistic regression equation which computes the conditional probabilities for the CK blood test and the coefficients for those coefficients is presented in Fig. 4. In that figure, the additional variable that accounts for the outcome of the CK test is referred to as CKABN. It takes on two values, namely, 1 for an abnormal CK reading and 0 for otherwise. The other variables are described in the figure. As indicated above, the processor module computes a probability for each value of

inverted or flat; (4) if the T-waves are elevated, by how much; and (5) whether both the STDEP and TWINV leads are non-zero.

Using the output of the waveform analyzer and previously entered values for other clinical variables, the processor module computes a probability that the patient has acute cardiac ischemia and the array of conditional probabilities that the system is configured to generate. This information is then printed on the top of the ECG printout in the manner described earlier.

The choice of the CK blood test and ETT was not meant to be limiting. There are other potential tests that could be included either in addition to or as alternatives to the CK blood test and ETT. For example, other tests that could be performed include: other blood tests such as troponin and myoglobin and radionucleide imaging tests, such as Sestamibi scanning, and other forms of exercise stress tests, just to name a few. Also, there are other ways in which to display the array of conditional probabilities. We have described a simple presentation. But more a complex tree or multiple trees of conditional probabilities could be generated. The added conditional probabilities, however, present greater challenges in communicating the information to the physician in an effectively and readily understandable manner.

The logistic regression equations mentioned above are presented as merely illustrative of one way in which the cardiac condition and the probabilities can be modeled. There are a variety of statistical methods and algorithms that can be used for calculating the predicted probability of an adverse cardiac event or a life threatening cardiac condition. These include, for example, artificial feed-forward multi layer neural networks and classification trees. Although the

cardiac condition based at least in part upon ECG information falls within the scope of this invention.

In addition, the diagnostic tool described above has applicability to many other medical problems beyond the above-described cardiac related problems. The extension to circumstances that are not cardiac related is straight forward. Such alternative embodiments would likely (but not necessarily) have a similar functional block diagram structure to that described above, except that a different diagnostic or monitoring instrument would be used in place of the electrocardiograph, and the system may or may not include a module which analyzes the output of the monitoring instrument before providing input to the predictive instrument portion.

The following are further examples of applications involving non-cardiac diagnoses or medical outcomes, along with their likely key clinical variables.

In the domain of vascular disorders, the regression equations for computing the probabilities of a pulmonary embolus would include among its key variables the same variables as listed above, and also heart rate and respiration rate, as well as a modification of the symptoms regarding the suddenness of onset, and also ECG variables related to right heart strain (e.g. relating to QRS complex and ST/T wave changes). Diagnostic tests for which conditonal probabilities would be important would include pulse oximetry P_aO_2 (oxygen concentration in the blood) and echocardiogram evidence of pulmonary hypertension and/or right ventricular strain, and other blood tests.

In the domain of neurologic disorders, the regression equations for computing the probabilities of a cerebral hemorrhage (i.e., hemorrhagic stroke) would include among their key variables the patient's hist[illegible] of medications (e.g. anticoagulants, etc.), prior h[illegible]

low), ECG abnormalities (as not showing a contrary cardiac cause for derangements in heart rate, blood pressure, respiratory rate and other findings in the form of an interaction term in the mathematical model) laboratory tests such as white blood count (either unduly high or unduly low), and other special blood tests typically available on-line from hospital clinical information systems. Also, other ongoing monitoring data relating to blood and other body fluid culture results, such as are typically available on electronic clinical information systems, are further important explanatory variables relating to the source of sepsis. Examples of additional tests on which conditional probabilities would be based would include blood interleukin levels, c-reactive protein, and pulse oximetry.

Each of the above diagnoses to be predicted have consequences in terms of clinical outcomes including, for example, mortality. Other outcomes that can be predicted by a predictive instrument include mortality due to acute myocardial infarction or congestive heart failure, as well as conditional outcomes such as are obtained from the thrombolytic predictive instrument (see U.S. 4,998,535). The use of this approach also applies to other non-cardiac conditions for which prediction of medical outcomes can be conditioned on the use of specific therapies.

The examples presented above are meant to be merely illustrative of the many ways in which the invention can be used to aid in the diagnosis of a patient's medical condition. It is not intended that the invention be limited to the few examples that were described here. In general, the invention covers any instrument which computes on the basis of a set of clinical features a probability of a medical outcome or diagnosis and an array of conditional probabilities

reflected in medical insurance claims, such as the mere performance of certain tests, the fact of hospitalization, the actual diagnostic code (e.g. the ICD9 Code), etc. A clinical feature is any piece of additional information about the patient, which when incorporated into a mathematical model predicts a given medical outcome.

A medical outcome or medical diagnosis, such as might be predicted by a predictive instrument, is defined in the following way. A medical outcome is the state of a patient defined in medical terms, typically described in the context of a particular constellation of presenting symptoms and clinical features. In practice, the outcome is selected to be clinically meaningful to the care of the patient. Therefore, an important medical outcome for a patient with a heart attack is mortality. For a person with respiratory failure, it is also mortality but it is also long-term respiratory disability, which might be defined, for example, as lack of ability to do activities of daily living due to shortness of breath as well. For a person with neurologic presenting symptoms, an important medical outcome is preservation of normal mental function as well as mortality.

There is overlap between the concept of medical outcomes and medical diagnoses. For example, when a decision has to be made about a patient, before the clinician can evaluate the likely ultimate outcome, the clinician must first consider the specific medical diagnosis or family of diagnoses that the patient has which require attention. Thus, a diagnosis is, in a sense, an intermediate "outcome". For a person coming to the emergency department with chest pain and/or other signs and symptoms, the first question on the clinician's mind is, what is the diagnosis? If the diagnosis, i.e.,

Claims:

1. A method for evaluating a medical condition of a patient, said method comprising:

monitoring one or more clinical features of a patient;

based on the monitored features, computing a primary probability of a medical outcome or diagnosis;

computing a plurality of conditional probabilities for a selected diagnostic test, said conditional probabilities including a first probability of the medical outcome or diagnosis assuming the selected diagnostic test produces a first outcome and a second probability of the medical outcome or diagnosis assuming the selected diagnostic test produces a second outcome; and

displaying the computed primary probability as well as the plurality of computed conditional probabilities to a user as an aid to determining whether to administer the selected diagnostic test to the patient.

2. The method of claim 1 wherein the step of monitoring comprises monitoring EKG-related characteristics of the patient, wherein the computed primary probability is a probability of a cardiac problem, and wherein the selected diagnostic test is selected from the group consisting of a CK blood test, an ETT, a stress test, and Sestamibi scanning test.

3. The method of claim 1 further comprising computing a second plurality of conditional probabilities for a second selected diagnostic test, said second conditional probabilities including a first probabil[illegible] of the medical outcome or diagnosis assuming the se[illegible]

6. A diagnostic apparatus for use with a patient, said apparatus comprising:

a monitoring device which during use monitors one or more clinical features of the patient;

an output device; and

a predictive instrument receiving input from the monitoring device and programmed to: (1) compute therefrom a primary probability of a medical outcome or diagnosis based on the monitored one or more clinical features; (2) compute a plurality of conditional probabilities for a selected diagnostic test, said plurality of conditional probabilities including a first probability of said medical outcome or diagnosis assuming the selected diagnostic test produces a first outcome and a second probability of said medical outcome or diagnosis assuming the selected diagnostic test produces a second outcome; and (3) display the computed primary probability along with the plurality of computed conditional probabilities on the output device.

FIGURE 2

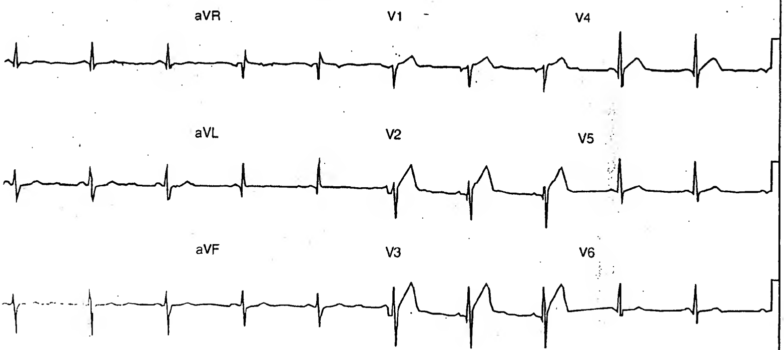
Name: John Doe
Age: 62 years
Sex: Male
Dx: Chest pain chief complaint

Rate	58	PREDICTED PROBABILITY OF ACUTE ISCHEMIA = 42%
PR	158	....based on age, sex, chest pain status (above);
QRSD	91	....anterior T waves flat or slightly inverted in two or more leads V1-V4
QT	415	
QTc	408	
--AXIS--		
P	28	
QRS	-37	
T	94	

IF CK *positive* PROBABILITY of AI = 85% - *no ETT* indicated
IF CK *negative* PROBABILITY of AI = 25% - *do ETT*

IF ETT *positive* PROBABILITY of AI = 40%
IF ETT negative PROBABILITY of AI = 3%

IF ETT *positive* PROBABILITY of AI = 70%
IF ETT negative PROBABILITY of AI = 20%



LXH 00000-0000 Speed: 25 mm.sec Limb: 10 mm/mV Chest: 10 mm/mV

FIGURE 4

Variable x_1	Definition	Coefficient (β_1)
CHPAIN	-1 chest pain present -0 not present	0.7006
SX1CP	-1 chest of left arm pain chief complaint -0 not primary complaint	1.5857
GENDER	-1 female -2 male	-0.2329
QWAVES	=1 ECG Q waves present	0.7665
STDEP	=2 ECG S-T segment depression 2 mm or more =1 ECG S-T segment depression 1-2 mm =0.5ECG S-T segment depression 0.5-1.0 mm =0 otherwise	0.5953
STEL	=2 ECG S-T segment elevation 2 mm or more =1 ECG S-T segment elevation 1-2 mm =0 otherwise	0.5481
TWINV	=2 ECG T- waves inverted 5 mm or more =1 ECG T- waves inverted 1-5 mm =0.5ECG T- waves inverted 0.5-1 mm =0 otherwise	0.5163
TWEL	=1 ECG T- waves elevated ("hyperacute")	0.9880
AGELT60	=40 for ages less than 40 =age -40 for age 40 to 60 =20 for ages greater than 60	0.0836
AGEGT60	=0 for ages less than 60 =age -60 for ages 60 or greater	0.0191
CKABN	=1 abnormal CK readings =0 otherwise	1.7708
Intercept	=1	-4.5597